333. *The Structure of Ginkgetin. Part II. New Syntheses of 5 : 8-Dihydroxy-4′-methoxyflavone.*

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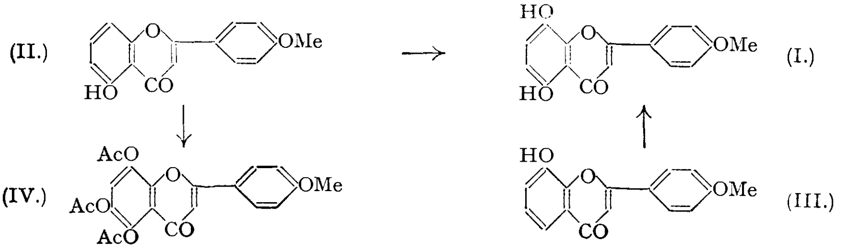
Pure 5 : 8-dihydroxy-4′-methoxyflavone (I) has been synthesised by the oxidation of both 5- and 8-*hydroxy-4′-methoxyflavone* with alkaline potassium persulphate.

Ginkgetin was supposed by Furukawa (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1932, **19**, 27; 1933, **21**, 278) to be 5 : 8-dihydroxy-4′-methoxyflavone (I), and the synthesis of this compound from 2 : 3-dihydroxy-6-methoxyacetophenone by the Allan–Robinson fusion method was described in Part I of this series (*J.*, 1948, 2138). This preparation, however, did not proceed smoothly, and (I) was not obtained completely pure. Alternative syntheses have, therefore, been carried out by applying the Elbs persulphate oxidation to 5-hydroxy-4′-methoxyflavone (II) and to 8-*hydroxy-4′-methoxyflavone* (III). Seshadri and his co-workers have used this reaction for the synthesis of a wide variety of hydroxylated 5 : 8-dihydroxyflavones and related compounds, by introducing a new hydroxyl group into position 8 of a 5-hydroxy-derivative (for bibliography and general discussion see Baker and Brown, *J.*, 1948, 2303), but the introduction of a hydroxyl group into position 5 of an 8-hydroxy-compound has not hitherto been effected.



Difficulty was experienced in preparing 5-hydroxy-4′-methoxyflavone (II) by fusion of 2 : 6-dihydroxyacetophenone with anisic anhydride and sodium anisate, followed by hydrolysis of the product, according to Syed and Wheeler (*J.*, 1936, 1714). These authors do not record the yield, but we find that it does not exceed 12%. When the fusion product was worked up without hydrolysis, it was found to contain 5-*hydroxy-4′-methoxy-3-anisoylflavone* in at least 85% yield. This compound is difficult to characterise owing to complicated polymorphic phenomena, but it readily yields a homogeneous *acetyl* derivative. Attempts were made to remove the 3-anisoyl group by alkaline hydrolysis under a variety of conditions using, *e.g.*, sodium carbonate or sodium hydroxide in aqueous alcohol, but the flavone was found to be very largely destroyed, and only very small quantities of the desired 5-hydroxy-4′-methoxyflavone (II) could be isolated. It is clear that rupture of the heterocyclic ring occurs more readily than hydrolysis of the 3-anisoyl group; this is contrary to general experience and to the very closely related case of 5-hydroxy-3-benzoylflavone which readily loses the benzoyl group alone by alkaline hydrolysis (Rajagopalan, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, 1947, **25**, 436).

Oxidation of 5-hydroxy-4′-methoxyflavone with potassium persulphate in alkaline, aqueous pyridine solution gave 5 : 8-dihydroxy-4′-methoxyflavone. The identity of this product with that previously prepared was confirmed by the mixed melting points of the diacetates and the dimethyl ethers. A by-product of the oxidation of (II) was isolated as its acetyl derivative; this is undoubtedly 5 : 6 : 8-*triacetoxy-4′-methoxyflavone* (IV) arising from the introduction of two hydroxyl groups; this appears to be the first recorded case of the introduction of two hydroxyl groups during the Elbs persulphate oxidation. The new groups are assumed to be in positions 6 and 8, *ortho* and *para* to the original hydroxyl group in position 5, because the intermediate phenyl potassium sulphate grouping in position 8 or 6 is likely to be weakly *ortho–para* directing compared with the free hydroxyl group in position 5.

5-Hydroxy-4′-methoxy-3-anisoylflavone was similarly oxidised to 5 : 8-*dihydroxy-4′-methoxy-3-anisoylflavone*, and in this case also a trihydroxy-compound was isolated as its acetyl derivative, which, for the above reasons, is assumed to be 5 : 6 : 8-*triacetoxy-4′-methoxy-3-anisoylflavone*.

8-Hydroxy-4′-methoxyflavone (III) was prepared by fusing 2 : 3-dihydroxyacetophenone with anisic anhydride and sodium anisate, and subsequently hydrolysing the product. When the fusion mixture was worked up without hydrolysis, two products were isolated, 8-*anisoyloxy*-4′-*methoxy*-3-*anisoylflavone* which could be hydrolysed to 8-hydroxy-4′-methoxyflavone, and a smaller amount of 8-*anisoyloxy*-4′-*methoxyflavone*. The formation of 3-acylflavones is a general feature of the Allan–Robinson method and was investigated by Baker (*J.*, **1933**, 1383). Oxidation of 8-hydroxy-4′-methoxyflavone (III) with potassium persulphate under the usual conditions gave 5 : 8-dihydroxy-4′-methoxyflavone (I), but in much smaller yield than by the oxidation of the isomeric 5-hydroxy-4′-methoxyflavone (II).

It may be noted that the melting points of pure 5 : 8-dihydroxy-4′-methoxyflavone (233·5—234°) and its diacetyl derivative (231·5°) are very close to those recorded by Furukawa (*loc. cit.*) for ginkgetin (238—240°) and diacetylginkgetin (226—228°). The dimethyl ethers of 5 : 8-dihydroxy-4′-methoxyflavone and of ginkgetin are, however, widely different, the former having m. p. 162·5° and the latter m. p. 225—227°.

EXPERIMENTAL.

5-*Hydroxy*-4′-*methoxy*-3-*anisoylflavone*.—2 : 6-Dihydroxyacetophenone (8 g.), anisic anhydride (40 g.), and sodium anisate (12 g.) were fused and stirred at 190—205° for 6 hours. The product was boiled with water (75 c.c.), ethyl acetate added under reflux until complete solution occurred, and the mixture cooled and then shaken with sodium carbonate (20 g.) and water (200 c.c.) for 18 hours. Filtration yielded brownish-yellow crystals (11·5 g.), m. p. 156—157·5°, and from the ethyl acetate layer were obtained yellow prisms (4·2 g.), m. p. 121—133°. These products were combined and recrystallised twice from ethyl alcohol (1 l.), giving yellow prisms (7·4 g.), melting at 151—152° to a cloudy fluid which cleared at 158°. Further crystallisation gave a mixture of bright yellow prisms, m. p. 160—161°, and pale yellow prisms of indeterminate melting point. The more compact, bright yellow prisms were separated by taking advantage of their rapid settling from alcoholic suspension, and on recrystallisation from alcohol gave the pale yellow prisms, m. p. *ca.* 152—154° [Found : C, 71·3; H, 4·4; OMe, 15·5. $C_{22}H_{12}O_4(OMe)_2$ requires C, 71·6; H, 4·5; OMe, 15·4%]. This 5-*hydroxy*-4′-*methoxy*-3-*anisoylflavone* is clearly polymorphic and exhibits a variety of melting points depending on the solvent used for its crystallisation, and on the temperature of the bath on introduction of the specimen. Apart from the form, m. p. 160—161° (usually obtained from ethyl acetate), two other melting points are observed in the neighbourhood of 142° and 174°. With an original bath-temperature of 100°, the substance (m. p. *ca.* 152—154°) undergoes partial melting at *ca.* 152° but does not clear till 174° ; with an original temperature of 135° it melts at *ca.* 173°; at 142° it melts rapidly and completely. The compound gives a transient green coloration with alcoholic ferric chloride, which rapidly changes to a brownish-purple.

5-*Acetoxy*-4′-*methoxy*-3-*anisoylflavone*.—The mixture of dimorphic forms of 5-hydroxy-4′-methoxy-3-anisoylflavone (1·5 g.) was heated under reflux for 5 hours with acetic anhydride (15 c.c.), excess of reagent was removed by distillation under diminished pressure, and the residue treated with water, yielding a homogeneous solid (1·45 g.), m. p. 218—219° without crystallisation. By dissolution in ethyl acetate (175 c.c.) and concentration (to 60 c.c.), colourless diamond-shaped prisms (1·2 g.), m. p. 220°, were obtained (Found : C, 70·5; H, 4·5. $C_{26}H_{20}O_7$ requires C, 70·3; H, 4·5%). Hydrolysis of this 5-*acetoxy*-4′-*methoxy*-3-*anisoylflavone* by boiling with a mixture of acetic and hydrochloric acid for half an hour readily regenerated the parent hydroxy-compound.

5 : 8-*Dihydroxy*-4′-*methoxyflavone* (I).—5-Hydroxy-4′-methoxyflavone (1 g., 1 mol.; m. p. 152—153°) was dissolved in a mixture of pyridine (20 c.c.) and water (30 c.c.) containing potassium hydroxide (1·05 g., 5 mols.), and to the stirred solution was added during 2 hours a solution of potassium persulphate (1·5 g., 1·5 mols.) in water (40 c.c.). After 24 hours the solution was acidified to Congo-red [unchanged 5-hydroxy-4′-methoxyflavone (0·45 g.) was thereby precipitated], and the filtrate was extracted twice with ether and then heated for half an hour on the water-bath after the addition of sodium sulphite (3 g.) and concentrated hydrochloric acid (35 c.c.). After the mixture had cooled, the yellow, crystalline solid (0·25 g.) was collected and crystallised four times from ethyl alcohol * (once with charcoal), giving fine, yellow prisms (0·1 g.), m. p. 233·5—234° (Found : C, 67·6; H, 4·5; OMe, 11·1. Calc. for $C_{15}H_9O_4{\cdot}OMe$: C, 67·6; H, 4·2; OMe, 10·9%). The diacetyl derivative formed colourless, microcrystalline prisms, m. p. 231·5° (from ethyl alcohol), which showed no depression of the melting point when mixed with 5 : 8-diacetoxy-4′-methoxyflavone, m. p. 230°, prepared as previously described by Baker and Flemons (*J.*, 1948, 2138). Further identification was provided by vigorous methylation, with methyl sulphate and potassium hydroxide in aqueous acetone, to 5 : 8 : 4′-trimethoxyflavone, m. p. and mixed m. p. with an authentic specimen (Baker and Simmonds, *J.*, 1940, 1373; Baker and Flemons, *loc. cit.*) 162·5°.

5 : 6 : 8-*Triacetoxy*-4′-*methoxyflavone* (IV).—The alcoholic mother-liquors from the crystallisation of the 5 : 8-dihydroxy-4′-methoxyflavone above * were evaporated and heated under reflux with acetic anhydride and a drop of pyridine for 1 hour. The solid precipitated on the addition of water was crystallised four times from alcohol (once with charcoal), giving colourless, microcrystalline prisms (17 mg.), m. p. 248—248·5° after sintering at 247° [Found : C, 61·9; H, 4·4; Ac, 34·7.† $C_{16}H_9O_3(OAc)_3$ requires C, 61·9; H, 4·2; Ac, 30·3%]. When mixed with 5 : 8-diacetoxy-4′-methoxyflavone, m. p. 230°, the melting point was *ca.* 218°. A larger quantity of this 5 : 6 : 8-*triacetoxy*-4′-*methoxyflavone* was isolated from a number of oxidation experiments, and, after twelve recrystallisations from alcohol, the fine needles had a constant m. p. of 253·5—254°. Hydrolysis to the trihydroxy-compound was attempted using acetic acid–hydrochloric acid, but the product darkened and was not isolated in the pure state; attempts to convert it into a flavoquinone by oxidation with *p*-benzoquinone were unsuccessful. The high value for the above acetyl determination † is typical of other cases (not quoted) in this series, and is undoubtedly due to breakdown of the heterocyclic nucleus under the conditions of the determination.

5 : 8-*Dihydroxy*-4′-*methoxy*-3-*anisoylflavone*.—A solution of 5-hydroxy-4′-methoxy-3-anisoylflavone

(2·5 g., 1 mol.) in water (32 c.c.) and pyridine (15 c.c.) containing potassium hydroxide (1·74 g., 5 mols.) was oxidised by the addition of potassium persulphate (1·68 g., 1 mol.) in water (60 c.c.), and the product worked up as in the case of the oxidation of 5-hydroxy-4′-methoxyflavone (above). The crude material (0·1 g.) was crystallised four times from ethyl alcohol (charooal), giving yellow prisms (30 mg.), m. p. 233·5—234° (Found : C, 66·9; H, 4·8. $C_{24}H_{18}O_7,H_2O$ requires C, 66·1; H, 4·6%). This 5 : 8-*dihydroxy-4′-methoxy-3-anisoylflavone* has the same melting point as 5 : 8-dihydroxy-4′-methoxyflavone, but a mixed melting-point determination showed a depression of 29°.

5 : 6 : 8-*Triacetoxy-4′-methoxy-3-anisoylflavone*.—The product contained in the alcoholic mother-liquors was acetylated with acetic anhydride and pyridine and, after four crystallisations from ethyl alcohol, the *triacetyl* derivative was obtained as colourless, short prisms (15 mg.), m. p. 214—215° (Found : C, 64·6; H, 4·5. $C_{30}H_{24}O_{11}$ requires C, 64·3; H, 4·3%).

2 : 6-*Dianisoyloxyacetophenone*.—This compound was previously isolated when attempting to prepare the monoanisoyl derivative of 2 : 6-dihydroxyacetophenone by interaction with 1 mole of anisoyl chloride in pyridine (Baker and Flemons, *loc. cit.*). By using 2·5 moles of the acid chloride, washing the crude product with aqueous sodium carbonate, and crystallising from alcohol, a 90% yield of the pure compound, m. p. 141°, was obtained. Molecular rearrangement to give 2-hydroxy-6-anisoyloxy-4′-methoxydibenzoylmethane could not be successfully carried out by heating with sodamide in toluene, or with potassium carbonate in toluene or pyridine.

8-*Hydroxy-4′-methoxyflavone* (III).—(*a*) 2 : 3-Dihydroxyacetophenone (4 g.; Baker and Smith, *J.*, 1936, 347), anisic anhydride (28 g.), and sodium anisate (4 g.) were stirred at 180—190° for 7 hours. The product was dissolved in alcohol (600 c.c.) and hydrolysed by heating under reflux for 10 minutes with a solution of potassium hydroxide (15 g.) in water (20 c.c.); the solution was then diluted with water (300 c.c.) and, after removal of the alcohol under diminished pressure, saturated with carbon dioxide. The solid thus obtained was dissolved in a solution of potassium hydroxide (2 g.) in water (80 c.c.), the solution shaken with ether, and the phenolic product reprecipitated by carbon dioxide. The 8-*hydroxy-4′-methoxyflavone* (III) was crystallised (charcoal), first from ethyl acetate and then from alcohol, giving fine, colourless needles (1·3 g.), m. p. 235° (Found : C, 71·2; H, 4·4; OMe, 11·4. $C_{15}H_9O_3{\cdot}OMe$ requires C, 71·6; H, 4·5; OMe, 11·6%). The *acetyl* derivative formed colourless needles, m. p. 166—167° (Found : C, 69·3; H, 4·2; OMe, 10·3. $C_{17}H_{11}O_4{\cdot}OMe$ requires C, 69·7; H, 4·5; OMe, 10·0%), from alcohol.

(*b*) 8-Anisoyloxy-4′-methoxy-3-anisoylflavone (0·9 g.; below) was dissolved in alcohol (75 c.c.) and boiled for 10 minutes with a solution of potassium hydroxide (0·2 g.) in water (2 c.c.). The solution was diluted with water (75 c.c.), freed from alcohol by distillation under diminished pressure, and saturated with carbon dioxide. The precipitated solid was collected and crystallised from ethyl alcohol, giving colourless needles (0·08 g.), m. p. 234·5°, undepressed by admixture with the material prepared according to method (*a*).

8-*Anisoyloxy-4′-methoxy-3-anisoylflavone and* 8-*Anisoyloxy-4′-methoxyflavone*.—2 : 3-Dihydroxyacetophenone (2 g.), anisic anhydride (14 g.), and sodium anisate (2 g.) were stirred at 180—190° for 7 hours. A solution of the product in hot ethyl acetate (100 c.c.) and water (20 c.c.) was cooled and shaken with a solution of sodium carbonate (10 g.) in water (100 c.c.) for 18 hours. The pale yellow solid which separated was collected (3·1 g.) and digested with boiling alcohol. From the alcoholic solution was obtained 8-*anisoyloxy-4′-methoxy-3-anisoylflavone*, which on further crystallisation separated as pale yellow plates (1·8 g.), m. p. 164—166° [Found : C, 71·5; H, 4·8; OMe, 18·2. $C_{29}H_{15}O_5(OMe)_3$ requires C, 71·6; H, 4·5; OMe, 17·4%]. The alcohol-insoluble 8-*anisoyloxy-4′-methoxyflavone* (0·6 g.) separated from ethyl acetate as colourless plates, m. p. 204—205° [Found : C, 71·6; H, 4·6; OMe, 15·9. $C_{22}H_{12}O_4(OMe)_2$ requires C, 71·6; H, 4·5; OMe, 15·4%].

5 : 8-*Dihydroxy-4′-methoxyflavone* (I) *from* 8-*Hydroxy-4′-methoxyflavone* (III).—To 8-hydroxy-4′-methoxyflavone (0·5 g.) dissolved in a solution of potassium hydroxide (0·6 g.) in water (25 c.c.) was added, with stirring, during ¾ hour, potassium persulphate (0·75 g.) in water (25 c.c.). After 24 hours at room temperature, the dark solution was rendered faintly acid to Congo-red, filtered from a brown solid, and extracted with ether. The aqueous solution was then heated on a water-bath (½ hour) with sodium sulphite (1·5 g.) and concentrated hydrochloric acid (20 c.c.) and then cooled, and the solid collected, washed, and crystallised twice from alcohol (charcoal). The 5 : 8-dihydroxy-4′-methoxyflavone (I) separated as bright yellow plates (14 mg.), m. p. 233·5—234° (Found : C, 67·0; H, 4·3. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·2%), undepressed when mixed with the specimen of the same m. p., prepared by the oxidation of 5-hydroxy-4′-methoxyflavone (above). The diacetyl derivative formed needles from alcohol, m. p. and mixed m. p. 232°.

2-*Hydroxy-3-anisoyloxyacetophenone*.—To a solution of 2 : 3-dihydroxyacetophenone (0·5 g.) in dry pyridine (10 c.c.) cooled in ice-salt, was added anisoyl chloride (1·68 g.), and the mixture was slowly allowed to reach room temperature. Next day it was added to excess of dilute hydrochloric acid, and the sticky solid collected and crystallised from methyl alcohol, giving faintly yellow aggregates of cubes showing parallel growth (0·26 g.), m. p. 152—153° (Found : C, 66·6; H, 4·9; OMe, 10·4. $C_{15}H_{11}O_4{\cdot}OMe$ requires C, 67·1; H, 4·9; OMe, 10·8%). It gives a purple colour with alcoholic ferric chloride.

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